July 21, 1971

Dr. Ntinos C. Myrianthopoulos —
Section on Epidemiology and Genetics
Perinatal Research Branch
National Institute of Neurological Diseases & Stroke
Bethesda, Maryland 20014

Dear Dino,

Thank you for the material on the sickle proposal and for the other background on the collaborate study.

I was glad to see that you were two steps ahead of me in thinking about this protocol. I have only a couple of rather minor comments:

Skin color does not strike me as a reliable way of estimating black ancestry in view of our dim understanding of the genetic mechanisms. Besides, it also introduces a lot of confounding with social factors because the phenotype is evident. One should at least couple this with an examination of the bloods for other markers, especially Duffy.

I hope birth weight is explicitly in mind within the heading of weight at specific ages.

My most important point is one to which I know you are already most sensitive, that is the desirability of getting the data out as much as possible for within kindred comparisons. When a sickler child is identified one should seek to type the siblings so that developmental comparisons can be made as between segregates within a single family. Similarly whenever possible you should look for the same as between sibling mothers. This will require more follow-up at the collaborating institutions but a few families would be worth much more than a great many scattered individual tests.

If this goes through conventional review procedures the application probably should have considerably more detail about the protocols for conducting specific comparisons and appropriate controls. It may seem silly to ask that of a group like yourself but study sections are notoriously unreliable in crediting good sense to their colleagues. Believe it or not I would advocate that you make specific reference to such obvious points as dividing the sickler children according to which parent was the source of the gene. And sickler mothers according to whether the offspring was or was not also positive. With such study sections it, in my experience, is impossible to be too meticulous in explaining detail that perhaps should be accepted as a matter of common sense. And of course, on the other side, we all know how often some of our esteemed colleagues have themselves goofed!

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On page 7, question 14 is going to elicit some nit-picking. About 55% of these children will be sicklers in either case, inheriting the gene either from a heterozygotes mother or an unselected father. It is not going to be easy to clear up all the cases of umbilical sickle cell by retrospective examination; it would of course be remarkable if this were manifest at birth when there should be a preponderance of hemoglobin F. As to question 13 are there really enough data in the records of the study to make it likely that you can answer such a question?

Sincerely yours,

Joshua Lederberg
Professor of Genetics

JL/rr